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Donor parity no longer a barrier for female-to-male hematopoietic stem cell transplantation

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Allogeneic hematopoietic stem cell transplantation (HSCT) is a widely applied treatment for disorders mainly involving the hematopoietic system. The success of this treatment depends on many different patient- and donor-specific factors. Based on higher CD34+ yields and superior clinical outcomes associated with the use of male donors, males are generally seen as the preferred HSCT donor. In addition, female donors are notorious for bearing memory type lymphocytes induced by previous pregnancies; such alloimmune cells may provoke unwanted immune reactions such as graft-vs.-host disease in transplant recipients. Consequently, many transplant centers try to avoid parous donors, particularly when searching the best unrelated donor for a male patient. We recently showed that parous women with female offspring have an anti-male directed tolerogenic immune status comparable to that of nulliparous donors.[1] As discussed in this article addendum, the sex of the donor's offspring combined with the presence of HY-specific T regulator cells are possibly better selection criteria than parity status per se.

Keywords: sex mismatched hematopoietic stem cell transplantation, graft-versus-host disease, donor pregnancy, T regulator cells, male microchimerism, HY minor histocompatibility antigens

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Donor Sex Affects Stem Cell Donation Results and the Risk of Donation-Associated Toxicities

Peripheral blood stem cells (PBSC) are nowadays the most common source of CD34+ cells used in HSCT. Regardless of graft type, a hematopoietic stem cell donation procedure generally causes more harm to female donors as demonstrated by a higher rate of acute toxicities, pain, fatigue, the need for a central venous catheter placement and prolonged hospitalization after PBSC or bone marrow collection.[2] Furthermore, female donors are less likely to meet the requested cell dose after G-CSF-induced CD34+ stem cell mobilization and subsequent PBSC harvest by apheresis.[3] CD34+ cell dose is a critical factor affecting outcome of unrelated PBSC transplantation.[4]

Donor Characteristics Affect Several HSCT Outcome Variables

While the importance of Human Leukocyte Antigen (HLA) matching between patient and donor has been extensively studied, only few studies have addressed the impact of donor characteristics such as donor age, sex and parity history on the overall survival of patients undergoing HSCT. In contrast to subsequently published data,[5] the results of a large retrospective study on allogeneic HSCT procedures performed in the US showed that donor age is the only non-HLA factor affecting overall and disease-free survival.[6] But already in the seventies, it was reported that bone marrow cells were less likely to engraft when patient and donor were sex mismatched. Subsequent research led to the identification of a variety of Y chromosome-encoded T cell epitopes, the so called HY minor

Histocompatibility (H) antigens. In sex mismatched HLA matched transplantation settings, ubiquitously expressed HY peptides can be recognized by female T cells in an HLA-restricted manner.[7] Memory type HY-specific T cells of female donor origin accumulate in male graft-vs.-host disease (GvHD)-affected skin[8] and HSCT patient-derived HY-specific T cell clones cause severe tissue damage in vitro when tested in skin explant assays.[9] These observations point out that HY is a clinically relevant transplantation antigen. Indeed, female donor/male recipient (FDMR) mismatching is an acknowledged risk factor for HSCT-associated complications such as GvHD and early/late non-relapse mortality as compared with other patient/donor combinations.[10] Based on these clinical observations, FDMR has been included in the European Group for Blood and Marrow Transplantation (EBMT) risk score which can assist in therapy decisions.[11] As the negative effect of FDMR is reported in both sibling and unrelated HSCT settings, it is perhaps not surprising that the frequency of this particular patient/donor combination has declined in the EBMT registry over the past 2 decades.[12]

One of the most disputed non-HLA factor influencing HSCT outcome is donor parity. Several studies have reported that recipients of grafts prepared from female donors who had undergone multiple pregnancies prior to donation display a significantly higher rate of acute or chronic GvHD when compared with recipients of grafts derived from male donors (reviewed in ref. 13). Pregnancy often leads to T and B cell alloimmunization induced by placental exchange of cells between mother and fetus. There is ample evidence that maternal alloimmune T cells specific for fetal inherited paternal antigens (IPA) persist for a long time after the delivery.[14,15] These IPA-specific T cells may end up in cellular products prepared from female donors. We and others have reported that parous women seem either sensitized or tolerant to their offsprings' IPA, i.e. HY, as reflected by the dominant presence of circulating cytotoxic T cells[15-19] or T regulator cells (Treg) respectively.[1,19] Of note, pregnancy-induced minor H antigen-specific T cells respond to the same immunogenic minor H antigen-derived peptides as the T cells which have been isolated from patients who developed complications after sex mismatched HSCT.[20] Thus, parous female HSCT donors form a highly heterogeneous population when looking at the phenotypic features of their anti-IPA alloimmune T cell repertoire.

HY-Specific T Cells are Established in Virtually All Adult Female Donors

While the pre-HSCT established alloimmune repertoire of a female donor may be advantageous in particular HSCT settings,[21,22] some reports have actually proposed to deliberately avoid the selection of parous donors whenever possible.[13] It is however questionable if simply labeling a donor as being parous or nulliparous correctly reflects a sufficient difference in alloimmunization status. There is increasing evidence that women may already be exposed to HY antigens in early childhood, for instance through transmaternal flow of cells derived from an older male sibling[23] or from a twin brother who vanished in utero[24]; both can lead to persistence of low levels of tissue-resident or circulating male sibling cells carrying HY antigens.[1] How the putatively life-long presence of male microchimeric cells, in combination with mucosal exposure to male proteins in sexually active women, affects the adult female immune system had never been addressed.

In our recently published study,[1] we assessed whether HY priming can occur independently of parity. Focusing on the detection of HY-specific T regulator cells in relation to pregnancy history and family background, we reported that HY-specific T regulator cells are predominantly present in women who do not have male offspring; this group included both nulliparous donors and parous donors with female offspring. The supremacy of Treg in preventing GvHD-associated alloimmune reactivity without compromising Graft-vs.-Leukemia responses has been demonstrated in murine HSCT models as reviewed.[25,26] Obviously, much more research needs to be done regarding the incidence and phenotypic characteristics of pregnancy-induced HY-specific Tregs in female HSCT donors and especially in the cellular products routinely prepared from these donors. In addition, we need to identify (surrogate) markers associated with the dominant presence of HY-specific Treg over their cytolytic counterparts. Nonetheless, our data challenge the current concept that it is sensible to generally avoid the selection of parous female donors or to select only a nulliparous donor for a male patient in case a male donor is unavailable. Provided that we can reliably and routinely measure the presence of HY-specific Treg in a more simplified read out than thus far used,[1,19] it should be feasible in the future to select female donors on the basis of prominent HY-specific Treg activity regardless of their pregnancy history.

Conclusion

Although transplant physicians involved in HSCT donor selection procedures obviously need to weigh many different donor- and patient-related variables in relation to the targeted number of CD34+ cells and desired clinical outcome, we hope that our latest findings[1] may encourage transplant centers and search coordinating units worldwide to reconsider their current donor selection strategy.[27] Our data also subscribe the need for routine collection of detailed information on the parity[4] and family history of female donors, in particular regarding the sex of the donors' offspring and older siblings.[28] Such information may help to explain the differences in reported data sets wherein the effect of donor sex and parity on outcome variables such as GvHD and overall survival after allogeneic HSCT is addressed.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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